

Citation for published version:

Guy, R 2016, 'Managing diabetes through the skin: Diagnostic devices', *Nature Nanotechnology*, vol. 11, no. 6, pp. 493-494. <https://doi.org/10.1038/nnano.2016.53>

DOI:

[10.1038/nnano.2016.53](https://doi.org/10.1038/nnano.2016.53)

Publication date:

2016

Document Version

Peer reviewed version

[Link to publication](#)

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DIAGNOSTIC DEVICES

Managing diabetes through the skin

Gold-doped graphene combined with a bilayer gold mesh and polymeric microneedles forms a wearable sweat-based patch for real-time monitoring of glucose levels and controlled drug delivery.

Richard Guy

The global increase in diabetes is a significant physical and economic burden. Reducing the pernicious morbidities of the disease requires effective control of blood sugar levels through a strict regimen of diet and drug treatment (e.g., insulin injection)¹. Presently, glucose levels in blood or interstitial fluid (the solution that bathes the tissue cells) is monitored by either “finger sticks” – a procedure in which a finger is pricked using a lancet to obtain a small amount of blood for testing – or insertion of sensors through the skin. These procedures are invasive and, consequently, adherence to glucose monitoring by diabetics is poor. The search for a minimally or non-invasive method has been intense but largely unsuccessful to date. Writing in *Nature Nanotechnology*, Dae-Hyeong Kim and colleagues at Seoul National University, the Institute for Basic Science in Seoul, MC10 Inc. in Cambridge, the University Texas, Austin, and the Advanced Institutes of Convergence Technologies in Gyeonggi-do, Korea, now report a ‘soft’ graphene-based electrochemical platform that combines real-time monitoring of blood sugar and controlled drug delivery for managing glucose levels².

The only minimally invasive technology for glucose monitoring to have received approval by the U.S. Food and Drug Administration was the GlucoWatch Biographer. The device combined an on-board glucose sensor with reverse iontophoretic extraction of an interstitial fluid sample through intact skin³. It was marketed briefly in the early 2000s but was commercially unsuccessful for various reasons. Nonetheless, the skin interface remains an attractive target for the development of less intrusive glucose monitoring devices. For example, the GlucoWatch paradigm has been revisited in a temporary, skin-worn tattoo configuration⁴ and, the detection of glucose in sweat (provoked either by local delivery of pilocarpine or by vigorous exercise) has revealed an alternative route to acquire glucose data that correlate with blood sugar levels^{5,6}.

The device designed by Kim and co-workers integrates components that capture sweat from the skin, sensors for glucose, pH, humidity, temperature and mechanical strain, and a microneedle drug delivery system that responds to heat. The array of sensors is patterned onto gold-doped graphene and inter-connected via a serpentine gold mesh. This combination of materials and arrangement enhances the electrochemical activity of graphene and confers analyte selectivity and sensitivity. The device is flexible, mechanically robust, semi-transparent and conforms to the skin. When sufficient sweat is generated, typically after 10-20 minutes when the relative humidity reaches 80%, glucose monitoring begins. This lag-time is consistent with that reported previously between blood glucose levels and those in the interstitial fluid and sweat^{6,7}. In the prototypical configuration illustrated in Figure 1, the graphene hybrid patch is electrically connected to a portable electrochemical analyser, which acts as a power source and controls the wireless transfer of the acquired data to a remote mobile device such as a smartphone or tablet.

The detection of hyperglycaemia – through the glucose and pH sensors - is the cue for actuating drug delivery from the device. The polymeric microneedles, which contain metformin (the drug commonly used to treat diabetes), are coated with a hydrophobic layer of tridecanoic acid. This layer protects the microneedles from moisture when inserted into the skin and prevents the premature release of metformin. When an elevated glucose level is detected, the heater embedded in the patch is triggered, warming the microneedles. Above the transition temperature of tridecanoic acid ($\sim 41^{\circ}\text{C}$), the underlying polymer is exposed to interstitial water and the drug is released. The quantity of metformin liberated in this way is step-wise and titratable by adjusting the number of microneedles in the device.

Kim and co-workers present a substantial body of experimental data to characterise the constituent parts of the new device and to support its dual function in glucose monitoring and diabetes therapy. Proof-of-concept in human subjects is shown by the detection of high blood sugar levels after a meal and its reversal following normal insulin secretion. Experiments with genetically diabetic mice unequivocally demonstrate that drug release upon thermal activation of polymer dissolution results in substantial lowering of blood sugar in these animals over the next several hours.

There remain some important questions to answer before the technology can be translated into practical use. For example, is continuous and reproducible function of the glucose sensor for 24 hours possible? Will the device report faithfully on glucose excursions when the wearer is actively sweating due to ambient temperature or vigorous exercise? How is a commercialised system to be configured; is it possible to identify the disposable/replaceable component(s)? And regulatory

agencies will most certainly ask whether and how frequently sensor calibration is required; and what is the sensitivity to hypoglycaemia, a particular problem in juvenile diabetics?

With the present design, it seems extremely unlikely that the daily adult dose of metformin can be delivered without an unfeasibly large number of microneedles and/or an unacceptably large patch. As with all transdermal delivery applications, whether passive or facilitated in some way, an essential criterion is that the drug is potent and that its daily dose is no more than a few milligrams. Nevertheless, it is probably safe to say that these issues are already being addressed and that other therapeutic strategies are being identified to complement the significant advances achieved in this work. Thus, while the Holy Grail of diabetes management – a non-invasive feedback system combining glucose monitoring and responsive drug delivery - is not yet quite at hand, Kim and co-workers have certainly moved the field nearer to this coveted prize.

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Figure 1| Schematic diagram of the integrated glucose monitoring and diabetes therapy system.

1) Sweat is accumulated in the patch and 2) glucose therein is monitored electrochemically on a graphene hybrid platform that also supports an array of other sensors (pH, humidity, mechanical strain). 3) In response to the detected glucose, actuation of thermo-responsive, polymeric microneedles is initiated, releasing an appropriate quantity of diabetes medication. 4) The graphene hybrid device connects electrically to a portable electrochemical analyser that acts as a power supply and controller that wirelessly transmits data to a remote mobile device.

